The role of frailty in the association between depression and somatic comorbidity: Results from baseline data of an ongoing prospective cohort study

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ABSTRACT

Background: Depression and physical frailty in older persons are both associated with somatic diseases, but are hardly examined in concert.
Objectives: To examine whether depression and physical frailty act independently and/or synergistically in their association with somatic diseases.
Design: Baseline data of an ongoing observational cohort study including depressed cases and non-depressed comparison subjects.
Settings: Netherlands Study of Depression in Older persons (NESDO).
Participants: 378 depressed older persons confirmed by the Composite International Diagnostic Interview (CIDI), version 2.1, and 132 non-depressed comparison subjects.
Methods: Multiple linear regression analyses adjusted for socio-demographic and life-style characteristics were conducted with the number of somatic diseases as the dependent variable and depression and physical frailty as independent variables.

Physical frailty was defined as ≥3 of the following characteristics, slowness, low physical activity, weight loss, exhaustion, and weakness.
Results: Depression and physical frailty did not interact in explaining variance in the number of somatic diseases (p = .57). Physical frailty, however, partly mediated the association between depression and somatic diseases, as the strength of this association decreased by over 10% when frailty was added to the model (B = 0.47, p = .003, versus B = 0.41, p = .01). The mediation effect was primarily driven by the frailty criterion exhaustion. Of the remaining frailty components, only slowness was associated with the number of somatic diseases; but this association was fully independent of depression.
Conclusions: Our results suggest that depression and physical frailty have common pathways towards somatic diseases, as well as unique pathways. As no high-risk group was identified (no significant interaction), mental health nurses should regularly monitor for physical frailty within their caseload of depressed patients.

What is already known about the topic?

•Depression, frailty and somatic diseases are highly prevalent in later life.
•Depression and frailty lead to the development of adverse health outcomes.
•Frailty can be successfully detected and monitored by nurses.

What this paper adds

•Frailty partly explains the association between depression and somatic diseases.
•Depression and frailty have common, as well as unique pathways towards somatic diseases.
•Frailty does not enhance the negative health effects that are already associated with depression.

1. INTRODUCTION

Depression not only deteriorates the symptom burden of chronic somatic diseases, but also places persons at higher risk of new-onset somatic diseases like cardiovascular diseases diabetes, overweight, and even cancer (Penninx et al., 2013). The wide range of somatic consequences of depression, as well as an increasing strength of these associations in later life, suggest common underlying mechanisms associated with accelerated ageing (McKinney and Sibille, 2012 and Verhoeven et al., 2013). Several explanations for the relationship between depression and somatic comorbidity can be put forward, such as an unhealthy lifestyle, non-compliance to treatment in case of existing somatic diseases, as well as physiological dysregulations like overactivity of the hypothalamic-pituitary-adrenal axis, autonomic nervous system dysregulation, and immune activation (Penninx et al., 2013, Révész et al., 2013). Interestingly, many of these explanations are also thought to be the basis of frailty. Frailty is a condition of increased risk of adverse health outcomes (Fried et al., 2001). This risk is presumed to be caused by a reduction of the reserve capacity of various physiological systems, due to declines in molecular, cellular and physiological systems of the aged body (Strandberg and Pitkala, 2007).

Negative consequences of depression, such as somatic comorbidity, may thus occur as a result of the development of frailty.
Depression, frailty and somatic morbidity are highly prevalent in later life, and their mutual relationship is complex. Meta-analytic studies have estimated that 10.7% in community dwelling elderly aged 65 and over meet the criteria for frailty (Collard et al., 2012) and between 1.8% and 9.3% for major depressive disorder (Beekman et al., 1999 and Luppa et al., 2012). Empirical data have shown that although frailty and depression share overlapping characteristics, both represent distinct syndromes (Mezuk et al., 2013). Similar to the bidirectional association between depression and somatic diseases, a recent review also pointed to a potential bidirectional association between depression and frailty (Mezuk et al., 2012). Interpretation remains difficult as all studies in this review relied on depression severity scales (prone to confounding by frailty) instead of formal diagnostic criteria.
Up until today, no research has been conducted into the triangle depression–frailty–somatic morbidity. In order to prevent somatic morbidity, knowledge of the interplay between depression and physical frailty is crucial. In outpatient mental health care, specialized nurses generally care for the most vulnerable patients among which those with chronic depression, frailty, physical disabilities and unhealthy life style. Mental health care nurses who care for depressed elderly are very capable of detecting frailty and monitoring the development of frailty (Markle-Reid et al., 2006 and Metzelthin et al., 2013). Moreover, effective frailty interventions to date are usually based on nursing skills, such as assistance in daily living and improving exercise frequency (Markle-Reid et al., 2011).
In this study, we first aimed to confirm that somatic diseases are more prevalent among depressed patients, compared to non-depressed controls. Secondly, assuming several physiological pathways potentially underlie both frailty and depression, we hypothesize that frailty is an explanatory factor (in statistical terms a mediator) of the association between depression and somatic disease. Furthermore, we will also explore a moderating effect of frailty that might be explained by a reinforcing effect of two underlying pathways when depression and physical frailty occur simultaneously. In order to avoid contamination between frailty and depression, frailty will be defined as physical frailty, as done by the frequently used Fried Frailty Index (FFI) of Fried et al. (Fried et al., 2001).

2. METHODS

Study participants came from NESDO (the Netherlands Study of Depression in Older persons). This cohort study consists of 378 depressed subjects with a current DSM-IV diagnosis of major depressive disorder (95%), minor depression (5.6%) or dysthymia (26.5%), of which 26.5% have two depressive disorders, and 132 non-depressed subjects, aged 60 through 93 years (Comijs et al., 2011).
Recruitment of depressed participants took place in five regions in the Netherlands. Participants were recruited from mental health institutes (both in- and outpatients) and from primary care, in order to include persons with late-life depression in various developmental and severity stages (Comijs et al., 2011). The non-depressed comparison group was recruited from primary care practices.
Persons with a clinical diagnosis of dementia, a Mini Mental State Examination-score (MMSE) under 18 or an organic or psychotic disorder were excluded, since the

course of depression in these persons will be largely determined by the primary disorder. Insufficient mastery of the Dutch language was also an exclusion criterion. All participants received written and oral information about the study and were competent to consent to participation. Written informed consent was obtained from the participants. The ethical review boards of the participating institutes approved of this study.
All participants underwent a baseline examination at one of the participating clinics or at the homes of the participants. This examination included an interview with internationally accepted, frequently used measures, among which measures of demographic variables, depression, somatic comorbidity and physical tests such as gait speed. Trained research professionals, mainly consisting of mental health care nurses and psychologists, conducted all interviews and physical examinations. Details of NESDO are described elsewhere (Comijs et al., 2011).

3. Measures

3.1. Depression

The Composite International Diagnostic Interview (CIDI), version 2.1 was used in order to determine the presence of depression (World Health, 1997). The CIDI is a structured interview that diagnoses psychiatric disorders in adults according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the criteria of the International Classification of Diseases-10 (ICD-10). The CIDI has high validity for depressive and anxiety disorders (Kessler et al., 2010 and Wittchen et al., 1991). To determine the research DSM-IV diagnosis of current minor depression, questions were added to the CIDI, as in Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008).
Severity of depression was measured by the well-validated 30-item self-rating Inventory of Depressive Symptomatology (IDS) (Rush et al., 1986).

3.2. Somatic comorbidity

Somatic comorbidity was assessed by Statistics Netherlands (Centraal Bureau voor de Statistiek, www.CBS.nl) questionnaire: a self-report questionnaire about the presence of chronic diseases. In order to enhance its reliability, the questionnaire was conducted by the interviewers. Compared to general practitioner information, the accuracy of self-reports of these diseases was shown to be adequate and independent of cognitive impairment (Kriegsman et al., 1996). We used the number of reported diseases (not necessarily under treatment) as a continuous variable. This variable included the following diseases or disease categories: lung disease (asthma, chronic bronchitis, pulmonary emphysema), cardiovascular disease (cardiac events, heart failure, heart infarction, cardiac arrhythmia, coronary heart disease, angina pectoris, vascular abnormalities), stroke, diabetes, arthritis/rheumatism (osteoarthritis, rheumatism), gastro intestinal disease (ulcer, irritable bowel syndrome, Crohn's disease, colitis ulcerosa, constipation), cancer, epilepsy and thyroid disease. Presence of separate diseases/categories was dichotomized (by present yes/no).

3.3. Frailty

Physical frailty was operationalized by the criteria of Fried et al. (Fried et al., 2001) Conform the criteria of Fried and colleagues (Fried et al., 2001), physical frailty is present if three out of the following five criteria are met: (1) slowness, (2) low physical activity, (3) weight loss, (4) exhaustion, and (5) weakness. In this study, we included frailty both as a dichotomized variable according to Fried et al. (2001), as well as a dimensional characteristics based on the number of criteria present (range 0–5).

Slowness was measured by a six metre walking test. For men ≤173 centimetres (cm) tall the cut off time was 9 s, for men >173 cm the cut off time was 8 s. The cut off time for this criterion for women with a height of ≤159 cm was 9 s, for women >159 cm the cut off time was 8 s (extrapolated from the data of Fried and colleagues) (Fried et al., 2001).

Low physical activity level was defined as no daily activities such as walking and gardening, or the performance of sports less than once weekly. The last-seven-days self-administered version of the International Physical Activities Questionnaire (IPAQ) (Craig et al., 2003) consisting of eight items, was used to collect the physical activity data.

The presence of unintentional weight loss or low body mass index was used for the weight loss criterion. The CIDI question about unwanted weight loss was used to determine the loss of a minimum of one kilogram a week, during two or more consecutive weeks. BMI was defined as weight in kilograms divided by height in metres squared. With a BMI of <18.5 kg/m^2 weight loss was also considered to be present.

Exhaustion (poor endurance and energy) was determined by two questions from the Center for Epidemiologic Studies – Depression scale (CES-D) (Radloff, 1997) similar to other studies (Avila-Funes et al., 2008, Drey et al., 2010, Fried et al., 2001, Kiely et al., 2009 and Ostir et al., 2004): “I felt that everything I did was an effort” and “I could not get going.” The items asked “How often in the last week did you feel this way?” and subjects responded on a four-point scale: 1 = rarely or never (<1 day), 2 = some or a little of the time (1–2 days), 3 = a moderate amount of the time (3–4 days), 4 = most of the time (5–7 days). Participants answering 3 or 4 to either of these two items were categorized as positive on this criterion.

A handgrip dynamometer was used to assess muscle weakness. Participants were asked to perform two squeezes with the dynamometer, using the dominant hand. The best performance, recorded as strength in kilograms, was used for analysis. Cut off scores were stratified by gender and BMI quartiles according to Fried et al. (2001) participants unable to perform the test were also considered weak.

A total of four participants (3 depressed, 1 non-depressed) had missing data on one frailty criterion (weakness criterion) and were excluded from analyses with frailty as a dimensional characteristic. Nonetheless, the dichotomised frailty status could be classified based on the available criteria (Collard et al., 2014).

3.4. Covariates

Potential confounders were selected a priori, based on their relationship with depression or frailty as well as with somatic diseases in general (Woods et al., 2005) and included socio-demographic variables (Bayat et al., 2011 and Luppa et al., 2012), and life-style characteristics (Barcelos-Ferreira et al., 2013).

Demographic data were collected during the interview (age, gender, partner status and educational level).
Lifestyle variables included smoking status, use of alcohol, physical exercise and BMI. Smoking status was divided into two categories: non-smoker and current smoker. The Alcohol Use Disorder Identification Test (AUDIT) is designed to detect hazardous and harmful alcohol consumption (Saunders et al., 1993). AUDIT score was divided into three categories, no alcohol use, moderate alcohol use and problematic alcohol use. These categories were based on the first two questions assessing the frequency drinking and the number of units taken on a typical drinking day. Physical exercise was measured with the IPAQ (Craig et al., 2003) by calculating energy expenditure based on sports and daily activities in MET minutes/week. METs are multiples of the resting metabolic rate and a MET-minute is computed by multiplying the MET score of an activity by the minutes performed. Missing values in the IPAQ questionnaire were imputed by mean scores of age-sex stratified samples (n = 90).

4. STATISTICAL ANALYSIS

Demographic and clinical characteristics of the participants with and without depression were compared using independent samples t-tests for normally distributed, continuous variables, nonparametric Mann Whitney U tests for skewed continuous variables, and χ^2 tests for categorical variables.
Multiple linear regression analyses were conducted to examine associations of the number of somatic diseases (dependent variable) with depression (independent variable) adjusted for socio-demographic variables (age, gender, educational level, partner status, income) and lifestyle factors (smoking status, alcohol use, BMI, and physical exercise). First, we checked whether the associations between depression and somatic comorbidity were dependent on frailty by including interaction terms between frailty and depression in the fully adjusted models. We tested both, frailty as a dichotomous characteristic (present yes/no) and as a dimensional variable based on the number of criteria present. A significant interaction term between depression and frailty (yes/no) implies that the association between depression and somatic diseases is different in patients with and without frailty. In case of a significant interaction term with the number of frailty criteria present, the association between depression and frailty differs among the different levels of frailty. Subsequently, it was tested whether frailty was an explanatory factor in the association between depression and somatic diseases by assessing whether B decreased with 10% or more when adding frailty to the fully adjusted model.
Subsequently, we performed in-depth analyses to examine whether identified effects were driven by individual frailty criteria as well as whether frailty effects could also be identified in explaining the presence of individual somatic diseases. First, we analyzed components of frailty in a linear regression analysis with the number of somatic diseases as the dependent variable and depression as the independent variable, in the fully adjusted model. Next, we assessed whether depression was associated with individual diseases (disease present yes/no) with logistic regression analysis with disease category as the dependent variable and depression as the independent variable. Only diseases that differed (in the unadjusted analysis) between depressed and non-depressed participants were analyzed. Frailty (both

dichotomized and continuous frailty) was evaluated as an explanatory factor of the association between depression and type of somatic disease.
All *p*-values were tested two-tailed and *p* values ≤.05 were considered statistically significant. Data were analyzed using Statistical Package of the Social Sciences (SPSS), version 20.0.

5. RESULTS

The mean age [standard deviation (SD)] of the 510 participants was 70.6 [7.3] years, and 64.9% was female. Table 1 presents the characteristics of both the depressed and non-depressed group. The two groups differed significantly with respect to educational level, partner status, prevalence of frailty, smoking status, depression severity, physical activity and somatic disease burden. Depressed persons suffered from more somatic diseases than the non-depressed persons. Regarding the type of disease, the two groups differed with respect to lung disease, stroke and gastrointestinal disease.

[TABLE 1]

5.1. Associations between depression, frailty and somatic diseases

Multiple regression analyses adjusted for sociodemographic and lifestyle characteristics showed that the number of somatic diseases (dependent variable) was associated with depression (*B* (SE) = 0.47 (0.16); *p* = .003) as well as with frailty (presence of frailty: *B* (SE) = 0.64 (0.17); *p* < .001; frailty dimensional: *B* (SE) = 0.27 (0.06), *p* < .001). Moreover, multiple logistic regression analyses adjusted for sociodemographic and lifestyle characteristics also revealed that depression (dependent variable) was significantly associated frailty (presence of frailty: OR = 2.9 [95% CI: 1.3–6.7], *p* = .012; frailty dimensional: OR = 2.2 [95% CI: 1.6–2.9]. *p* < .001).

5.2. Frailty as a moderating factor

Whether the association between depression and number of somatic diseases was dependent on frailty status, was examined by adding the interaction term of depression by frailty to the fully adjusted linear regression models. Depression neither interacted with the presence of frailty (yes/no) (*p* = .57), nor with the number of frailty components present (*p* = .25).

5.3. Frailty as an explanatory factor

In order to examine whether frailty was an explanatory factor of the association between depression and somatic diseases, frailty was added to the different (fully adjusted) regression models that regarded the association between depression and somatic diseases (see Table 2, models 2a–2g). Adding the presence of physical frailty (yes/no) to the linear regression model reduced the association between depression and somatic diseases by 14.7%, indicating that frailty explained a substantial part of the association between depression and somatic diseases. Nonetheless, the association between depression and somatic diseases remained

significant, indicating an association between depression and somatic diseases independent of frailty. Comparable effects were found when frailty was added as a continuous variable.

[TABLE 2]

5.4. In-depth analyses

Only the frailty criteria “exhaustion/poor energy” and “slowness” were associated with the number of somatic diseases. In the depressed group 45.8% reported exhaustion/poor energy and 26.5% was slow, compared to 3.8% and 18.9% respectively in the non-depressed group. Of these two criteria, exhaustion/poor energy mediated the association between depression and somatic diseases, whereas the effect of slowness was fully independent of the presence of depression (see Table 2).
With regard to individual categories of somatic diseases, only lung disease, stroke and gastro intestinal disease were univariately associated with the presence of depression (Table 1). After adjustment for potential confounders, however, only stroke remained significantly associated with depression in our study (see Table 3). Subsequently, we tested whether this association was mediated by frailty. However, the presence of frailty (yes/no) was not identified as an explanatory factor in the relation between depression and stroke (see Table 3). Nonetheless, when frailty was entered as a continuous variable, it was an explanatory factor of the association between depression and stroke (see Table 3).

[TABLE 3]

6. DISCUSSION

As expected, somatic diseases were more prevalent among depressed patients than in the non-depressed comparison group (Knol et al., 2006 and Nicholson et al., 2006). Confirming our hypothesis, an accumulation of frailty characteristics, such as the frailty criteria of Fried et al. (2001) indeed partly explained the relation between depression and the number of somatic diseases. Since depression and frailty remained associated with the number and presence of somatic diseases, independently of each other, our results imply that depression and frailty have common relations with somatic diseases as well as unique relations. As frailty did not moderate the relation between depression and somatic diseases (interaction), the presence of frailty does not aggravate the negative health effects already associated with the depression itself.

6.1. Frailty as explanatory factor

Although physical frailty defined by the criteria of Fried et al. (2001) partly explained the association between depression and somatic diseases, this effect was primarily driven by the criterion “exhaustion/poor energy”. This is not surprising, as the operationalization of the criterion is based on two items of a depression severity scale, i.e. the Center for Epidemiological Studies – Depression scale (CES-D). This overlap between operationalization of frailty and depression probably explains its

mediating effects (in clinical terms). Even attempts to define frailty in pure biomedical terms thus still overlap with depression, stressing the need to measure both mental illness and frailty simultaneously when trying to evaluate long-term negative health outcomes. This approach can help us disentangle unique effects of depression and frailty.

The fact that of the other four frailty criteria, only slowness (or gait speed) was associated with the number of somatic diseases is an interesting finding. This association was completely independent from the presence of depression, implying that gait speed does have underlying pathophysiological mechanisms leading to somatic diseases or vice versa, which are different from mechanisms associated with depression. Gait speed as well as handgrip strength are the only two performance-based frailty criteria, and both have also been used as simplified measures of frailty in other studies (Cesari et al., 2005 and Syddall et al., 2003). Our results suggest that when studied in concert with depression, gait speed may be preferred to disentangle the relationship between frailty, depression and somatic diseases. Interestingly, gait speed can be quantified as done in our study, but mental health nurses can also easily observe gait speed. These observations and especially changes in gait speed, may trigger nurses for further assessment and treatment.

The discussion about how frailty should be operationalized is ongoing (Collard et al., 2012). When interested in pathophysiological mechanisms that are involved in both depression and physical frailty, the Fried Frailty Index can be used, but a simple measure of “vital exhaustion” may be even better. The pathophysiological mechanisms underlying vital exhaustion probably explain the shared impact of depression and frailty with respect to the negative health outcomes. This is in line with findings from a recent review, where it was stated that atypical depression, that is characterized by exhaustion, is more related to biological dysregulations than the melancholic subtype of depression (Penninx et al., 2013). Both the depression and the biological dysregulations may lead to somatic health decline (Penninx et al., 2013). The shared pathway may lead to the hypothesis that shared mechanisms may fully account for the negative health effects of depression. Nonetheless, this seems unlikely, as depression also remained independently associated with the number of somatic diseases and it has been shown before that the relation between depression and frailty is not fully explained by overlap between these two syndromes (Collard et al., 2014).

6.2. Clinical relevance

Depression is a highly prevalent condition among elderly and recurrence or relapse are not uncommon (Cole et al., 1999). Since frailty is a potentially reversible factor (Woods et al., 2005), of which the negative health impact can be reduced by specific interventions, assessment of frailty in depression is relevant for clinical practice. The other way around, somatic comorbidity is often accompanied by depression and in those cases associated with increased levels of disability (Lenze et al., 2001). Nurses are particularly likely to be caring for persons with chronic somatic diseases (Coster and Norman, 2009) and their work also requires knowledge of depression and frailty as well as their reciprocal relations with somatic diseases. Better recognition of frailty in older patients suffering from depression and/or chronic somatic conditions by nurses is also important, as nurse-led health promotion to frail older adults enhances quality of life, while not increasing the overall health care costs (Markle-

Reid et al., 2006 and Markle-Reid et al., 2011). This implies the need for a constant state of alertness towards the severity of frailty in depressed patients by nurses treating depressed elderly. Regarding this, it is noteworthy that simple screening tools for daily practice are available to confirm the presence of frailty (Ensrud et al., 2008).

6.3. Strengths and weaknesses

Some strengths and limitations of this study have to be mentioned in order to allow proper interpretation of the results. Whereas other studies use questionnaires as a substitute for depression diagnosis, this study used a formal diagnosis of depression according to DSM-IV criteria. This is an important strength of our study as formal criteria of depression are less prone to confounding by symptoms or signs of somatic diseases and frailty compared to (self-report) questionnaires assessing depressive symptoms. Furthermore, our findings also point to the importance of physical frailty within a psychiatric sample. Since participants were recruited from primary care as well as in- and outpatient secondary care clinics, this sample covers a large spectrum of depressive disorders. The fact that we did not find strong results for a one or two specific chronic diseases, adds to our hypothesis of general underlying pathways relating depression and frailty towards different somatic comorbidity. Nonetheless, we must acknowledge that due to low prevalence rates of some of the individual diseases, statistical power is probably too low for more definitive conclusions. Another limitation might be that somatic diseases were assessed by a self-report measure which may have led to bias, however previously the reliability of this questionnaire has shown to be adequate (Kriegsman et al., 1996).
Finally, as with any cross-sectional design it is not appropriate to draw causal conclusions. The relation between depression, frailty and somatic comorbidity is a complicated one, with reciprocal associations between all entities, and possibly other factors influencing these associations. Therefore, the relation between depression, frailty and somatic comorbidity should be further examined in prospective designs.

6.4. Final conclusion

This study confirms the relation between depression and somatic comorbidity. Frailty partly explains this relationship, but depression also remains an independent determinant of the somatic condition. As the prevalence of frailty is almost three times higher among depressed older persons compared to non-depressed persons (Collard et al., 2014), our findings argue for integral assessment of frailty in depressed older persons and mental health nurses should regularly monitor for physical frailty within their caseload of depressed patients. Analogue to the impact of frailty on the course of somatic diseases (Partridge et al., 2012 and Vaz Fragoso et al., 2012), the presence of frailty in depression probably also complicates the course and treatment of late-life depression. This, however, should be subject to further study, as well as future projects examining whether the effects of (nurse-led) interventions to prevent or reduce frailty in depressed older adults indeed improves both depression outcome and the negative health effects of depression.

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TABLES

Table 1.: Sample characteristics and differences between amount and type of somatic diseases.

Characteristics	Depressed group (*N* = 378)	Comparison group (*N* = 132)	*p*-Value and
Age, mean (SD), y	70.7 (7.4)	70.1 (7.2)	.371
Female gender, %	66.1	61.4	.322
Married or with partner, %	52.4	75.0	**<.001**
Education, mean (SD), years	10.4 (3.4)	12.5 (3.5)	**<.001**
Frailty according to Fried, %	27.0	9.1	**<.001**
Smoking, %			**<.001**
Non smoker	29.9	31.8	
Former smoker	42.9	59.8	
Smoker (<20)	19.3	6.8	
Heavy smoker (≥20)	7.1	1.5	
Alcohol use, %			**<.001**
No alcohol use	39.7	12.9	
Moderate alcohol use	50.5	63.6	
Problematic alcohol use	8.7	20.5	
IDS score, mean (SD)	30.1 (13.0)	7.8 (6.4)	**<.001**
BMI, mean (SD)	27.0 (4.6)	26.3 (4.1)	.138
Physical exercise: MET minutes/week, mean (SD)	2391 (2460)	3324 (2909)	**<.001**
Walking speed, s/6 m	7.7	6.9	**.025**
Hand grip strength, kg	27.2	30.2	**.007**
Chronic diseases, mean (SD)	2.1 (1.5)	1.5 (1.1)	**.001**
Type of disease, %			
Lung	15.3	7.6	**.023**
Cardiovascular	29.9	24.2	.215
Stroke	11.4	2.3	**.002**
Diabetes	12.7	18.2	.119
Arthritis/rheumatism	52.4	47.7	.343
Cancer	19.6	18.9	.863
Gastro-intestinal	14.0	6.8	**.029**
Epilepsy	1.3	0.0	.184
Thyroid	10.3	6.1	.143

Abbreviations: IDS, Inventory of Depressive Symptomatology; BMI, body mass index.

a. Comparison using analyses of variance (continuous variables), χ^2 statistics (categorical variables) and *U* tests (continuous, skewed variables).
b. Level of significance $p <. 05$.

Table 2. Depression and frailty as determinants of the total number of somatic diseases.[a]

	***B* (SE)**	**Beta**	***p*-Value [d]**	**Δ*B***
Model 1[b]				
Depression	0.484 (0.161)	.15	**.003**	
Model 2a[c]				
Depression	0.413 (0.159)	.13	**.010**	−14.7%
Frailty (yes/no)	0.590 (0.166)	.17	**.001**	
Model 2b[c]				
Depression	0.333 (0.163)	.10	**.041**	−31.2%
Number of frailty components	0.243 (0.061)	.21	**.001**	
Model 2c[c]				
Depression	0.473 (0.165)	.14	**.004**	−2.3%
Frailty: weight loss criterion	−0.003 (0.150)	<−.01	.983	
Model 2d[c]				
Depression	0.485 (0.161)	.15	**.003**	+0.2%
Frailty: hand grip strength criterion	0.191 (0.158)	.06	.225	
Model 2e[c]				
Depression	0.254 (0.167)	.08	.129	−47.5%
Frailty: exhaustion/poor energy criterion	0.552 (0.140)	.18	**.001**	
Model 2f[c]				
Depression	0.467 (0.158)	.14	**.003**	−3.5%
Frailty: slowness criterion	0.632 (0.161)	.19	**.001**	
Model 2g[c]				
Depression	0.474 (0.160)	.14	**.003**	−2.1%
Frailty: low activity level criterion	0.105 (0.149)	.04	.481	

a. Multiple linear regression analyses with number of somatic diseases as the dependent variable, adjusted for age, sex, years of education, partner status, average income, smoking status, alcohol consumption, physical activity and body mass index.
b. Model 1: Association between depression and the number of somatic diseases.
c. Model 2: Independent effect of depression and frailty (different definitions) added simultaneously in one linear regression analyses with the number of somatic diseases as the dependent variable.

d. Level of significance $p <. 05$.

Table 3. Depression and frailty as determinants of individual somatic disease categories.[a]

	OR (95% C.I.) (SE)	***B***	***p*-Value** [d]	**Δ*B***
Lung disease				
Model 1[b]				
Depression	0.50 (0.21, 1.22)	−0.687	.130	
Stroke				
Model 1[b]				
Depression	0.29 (0.08, 1.00)	−1.255	**.049**	
Model 2[c]				
Depression	0.34 (0.10, 1.23)	−1.068	.100	−14.9%
Number of frailty components	1.30 (0.97, 1.76)	0.264	.083	
Gastro-intestinal disease				
Model 1[b]				
Depression	0.45 (0.19, 1.05)	−0.802	.065	

a. Multiple logistic regression analyses with type of somatic disease as the dependent variable, adjusted for sociodemographic and lifestyle characteristics.
b. Model 1: Adjusted association of depression (independent variable) and type of somatic disease
c. Model 2: Independent effect of depression and frailty when added simultaneously in one logistic regression analyses with the type of somatic disease as the dependent variable.
d. Level of significance $p <. 05$.